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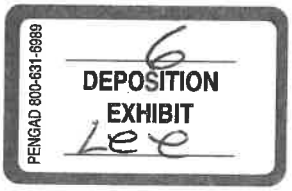
Review Article

Opioid Therapy for Chronic Pain: Overview of the 2017 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline



Jack M. Rosenberg, MD,* Brandon M. Bilka, MD,† Sara M. Wilson, MD,† and Christopher Spevak, MD, MPH, JD†

*Department of Veterans Affairs, Physical Medicine and Rehabilitation, Ann Arbor, Michigan; †Walter Reed National Military Medical Center, Bethesda, Maryland, USA

Correspondence to: Jack M. Rosenberg, MD, Department of Veterans Affairs, Physical Medicine and Rehabilitation, VA Ann Arbor Health System, Station 112A, 2215 Fuller RD, Ann Arbor, MI 48105, USA. Tel: 734-845-5919; Fax: 734-845-5847; E-mail: jackrose@umich.edu.

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Abstract

Description. The US Department of Veterans Affairs (VA) and US Department of Defense (DoD) revised the 2010 clinical practice guideline (CPG) for the management of opioid therapy for chronic pain, considering the specific needs of the VA and DoD and new evidence regarding prescribing opioid medication for non-end-of-life-related chronic pain. This paper summarizes the major recommendations and compares them with the US Centers for Disease Control and Prevention (CDC) guideline for prescribing opioids.

Patient Population. This Opioid Therapy CPG was developed for VA-DoD service members, veterans, and their families.

Methods. The VA/DoD Evidence-Based Practice Work Group convened a VA/DoD guideline renewal development effort and conformed to the guidelines established by the VA/DoD Joint Executive Council (JEC) and VA/DoD Health Executive Council (HEC). The panel developed questions, searched and evaluated the literature, developed recommendations using GRADE methodology, and developed algorithms. Passage of the CARA Act by Congress compelled consideration and comparison with the CDC opioid therapy guideline mid-development.

Results. There were 18 recommendations made. This article focuses on guideline development and key recommendations with CDC comparisons taken from four major areas, including:

- **initiation and continuation of opioids;**
- **type, dose, follow-up, and taper of opioids;**
- **risk mitigation;**
- **acute pain.**

Conclusions. Guideline development and recommendations are presented. There was substantial overlap with the CDC opioid guideline. Additionally, there were items particularly relevant to the VA-DoD, including risk mitigation, suicide prevention, and preventing opioid use disorder in young patients. Our guideline highlights avoiding opioid therapy longer than 90 days as a critical juncture.

Key Words. Guideline; Veterans; Opioids

Introduction

The treatment or diagnosis of pain is the reason for one out of five of health care office visits, accompanied by opioid prescribing in 20% of visits in 2010 compared with 11% in 2000 [1]. The increase in opioid prescribing is matched by a parallel increase in morbidity, mortality, opioid-related overdose death rates, and substance abuse treatment admissions [2]. This public health issue, which has been labeled an epidemic [3,4], is a critical issue for the US Department of Veterans Affairs (VA) and the US Department of Defense (DoD). In October 2015, the VA/DoD began working on an evidence-based clinical practice guideline for opioid therapy in treating chronic pain to replace the previous clinical practice guideline from 2010. The US Centers for Disease Control and Prevention (CDC) "Guideline for Prescribing Opioids for Chronic Pain" was released in 2016 [3].

Guideline Development Process

Recommendations were developed utilizing the quality standards and process in the "Guideline for Guidelines" published by the Evidence-Based Practice Working Group (EBPWG) [5]. At the start of the guideline development, all team members were required to submit conflict of interest (COI) disclosure statements for relationships in the prior 24 months. Verbal affirmations of no COI were used periodically during the development process. Web-based surveillance, such as ProPublica, was used to monitor for potential COIs. No Work Group members reported relationships and/or affiliations that had the potential to introduce bias, and none were found throughout the development of the guideline.

The EBPWG selected two guideline panel champions (cochairs), one each from the VA and DoD. The champions then selected a multidisciplinary panel of practicing clinician stakeholders. The specialties and clinical areas of interest included: Addiction Medicine, Anesthesiology, Family Medicine, Geriatrics, Internal Medicine, Mental/Behavioral Health, Neurology, Nursing, Pain Management, Palliative Care, Pharmacy, Physical Medicine and Rehabilitation, Physical Therapy, and Social Work.

The VA/DoD contracted with The Lewin Group, a third party with expertise in clinical practice guideline development, to facilitate meetings and develop key questions (KQs) using the population, intervention, comparison, outcome, time, and setting (PICOTS) format. A systematic review of the literature was conducted by the ERCI Institute addressing the key questions.

A Patient Focus Group explored patient perspectives on a set of topics related to management of opioid therapy (OT) in the VA and DoD health care systems, including knowledge of OT and other pain treatment options, delivery of care, and the impact of and challenges with OT and chronic pain.

The guideline panel developed nine KQs focusing on clinical topics considered to be the most clinically important and relevant with respect to long-term opioid therapy (LOT) for chronic pain. These included investigating how LOT compares with alternative pain modalities with regard to effectiveness and safety, while also evaluating the effectiveness and safety of various opioid formulations. The group also considered evidence to identify what factors increase the risk of developing misuse or opioid use disorder and investigated which medical or mental health conditions are absolute or relative contraindications to prescribing LOT. The group considered evidence relating to the use of additional medications concurrently with OT. The group also investigated the effectiveness of risk mitigation strategies and the safety and effectiveness of both treatment of opioid use disorder (OUD) and different tapering strategies and schedules.

The work group conducted a systematic search of peer-reviewed literature through January 2016 in order to find evidence relevant to the KQs. Emphasis was placed on randomized trials, systematic reviews, and meta-analyses of at least fair quality. The guideline panel rated recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method [6–8].

On July 22, 2016, the Comprehensive Addiction and Recovery Act was signed into law, requiring among other things that the CDC opioid guideline be considered in drafting this document. As a result of this review process, two additional KQs were addressed, one concerning naloxone rescue as a risk mitigation strategy and the other addressing the effect of prescribing acute opioid pain medications on the development of problems related to LOT.

As this guideline was a renewal, all prior recommendations from the 2010 guideline were considered for acceptance, modification, or removal, as explained in the guideline for guidelines reference document [5]. A refreshed evidence review was not performed for these 2010 recommendations.

The draft guideline was posted on a wiki website for a period of 14 business days for peer review and comment. The peer reviewers comprised individuals working within the VA and DoD health systems as well as experts from relevant outside organizations. Comments were considered and incorporated according to panel consensus. Final recommendations are focused on initiation and continuation of opioids, type, dose, duration, follow-up, and taper of opioids and risk mitigation.

The full guideline can be found at http://www.healthquality.va.gov/guidelines/Pain/cot/.

Recommendations

The guideline focuses on opioid therapy implementation as well as robust risk reduction. The guideline panel developed four one-page algorithms modeled on the 2010

algorithms. Figure 1 is an example of one of the algorithms and provides recommendations on determination of appropriateness for opioid therapy, with the initial recommendation that nonpharmacologic and nonopioid pharmacologic therapies be initiated over opioid therapy for chronic pain. Table 1 summarizes all 18 recommendations. Of all the recommendations, this paper highlights a few of the more unique areas of clinical importance.

Initiation of Opioid Therapy

Recommendation 1

a. We recommend against initiation of long-term opioid therapy for chronic pain. (Strong against)
b. We recommend alternatives to opioid therapy such as self-management strategies and other nonpharmacological treatments. (Strong for)
c. When pharmacologic therapies are used, we recommend nonopioids over opioids. (Strong for)

There is a rapidly growing understanding of the significant harms of LOT even at low doses (see the *Dose, Follow-up, and Taper of Opioids* section), including overdose and opioid use disorder (OUD). At the same time, there is a lack of high-quality evidence that LOT improves pain, function, and/or quality of life. When considering the benefits of LOT, it is important to consider whether LOT will result in clinically meaningful improvements in function such as readiness to return to work/duty and/or measurable improvement in other areas of function. The literature review identified no high-quality studies evaluating the efficacy of LOT for outcomes lasting longer than 16 weeks. Given the lack of evidence showing sustained functional benefit of LOT and moderate evidence outlining harms, nonopioid treatments are preferred for chronic pain.

Psychological therapies (e.g., cognitive behavioral interventions such as cognitive behavioral therapy [CBT] and biofeedback), exercise, and multidisciplinary biopsychosocial rehabilitation have been found to be effective for pain reduction in multiple pain conditions [9–11]. These interventions are safe and have not been shown to increase morbidity or mortality. While exercise and psychological therapies have not been compared directly with LOT, there is clear evidence that LOT has significant evidence for harm, even at low doses, that escalates with increasing dose. There is insufficient evidence to recommend psychological over physical therapies or vice versa; the choice of CBT, exercise, and/or biopsychosocial rehabilitation should be individualized based on patient assessment and a shared decision-making process [12].

In addition, nonopioid pharmacologic agents should be tried and optimized before consideration of opioid medications. Unless contraindicated, nonsteroidal anti-inflammatory drugs (NSAIDs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to be beneficial for chronic pain [10]. Other nonopioid medications should also be considered before opioids given the significant morbidity and mortality associated with opioid analgesics at even relatively low doses. As this is a LOT guideline and not a pain guideline, the potential harms of nonopioid therapy were not quantified and compared with LOT.

This recommendation was given a STRONG grade because of the moderate evidence showing definite harms in the way of deaths, overdoses, and development of OUD. Based on the evidence, it was considered that opioid therapy should no longer be given when all nonopioid approaches fail due to the substantial risk of harms.

The CDC guideline states, "Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patients." Our guideline takes a stronger stance against opioid therapy, largely driven by the risk for development of opioid use disorder. Both guidelines find little evidence of benefit for long-term opioid use.

Duration of Opioid Therapy

Recommendation 2

If prescribing opioid therapy for patients with chronic pain, we recommend a short duration. (Strong for)

Note: Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits.

The pillars for this recommendation are a paucity of research showing benefit for LOT, the strength of the evidence demonstrating the potential for life-threatening harm, and the substantial heightened risk for developing OUD in patients who receive OT beyond 90 days.

Two studies of chronic noncancer pain (CNCP) patients support the strong advisement being made in this recommendation. Edlund et al. (2014) [13] examined the claims data from a health insurance database between 2000 and 2005 to examine factors predictive of developing OUD. They found that, even greater than opioid dose, duration of OT was the strongest predictor of developing OUD. The odds ratio (OR) of developing OUD ranged from 14.92 for low-dose chronic prescriptions to 122.45 for high-dose chronic opioid administration. A second study by Boscarino et al. (2011) [14] examined medical records from a large health care system. Through interviews with a random sample of patients on LOT, they examined factors associated with and the prevalence of OUD (using the *Diagnostic and Statistical Manual of Mental Disorders* [DSM] *4* and *5* criteria). These results showed that the prevalence of lifetime

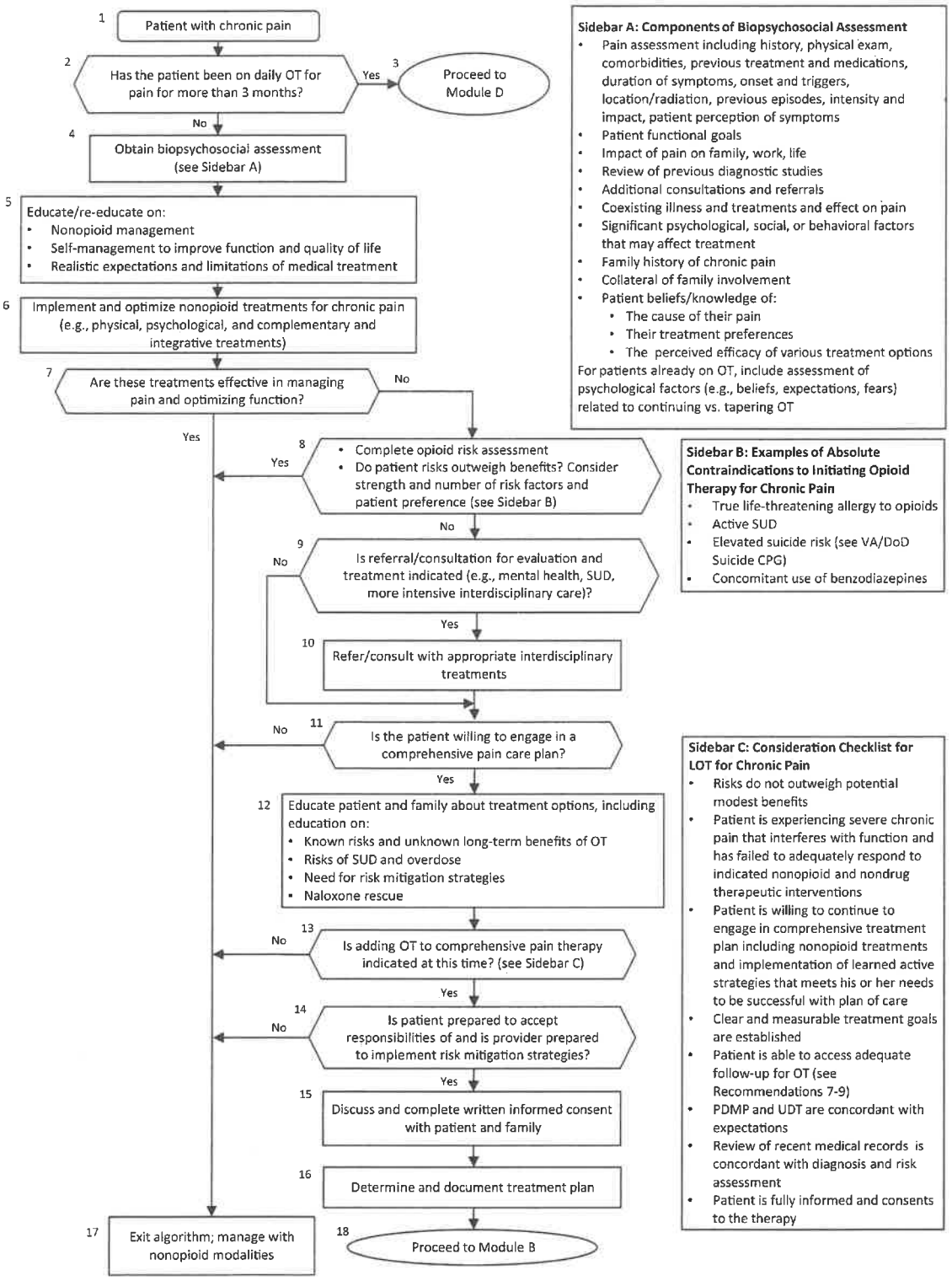

Figure 1 Determination of appropriateness for opioid therapy. Note: Nonpharmacologic and nonopioid pharmacologic therapies are preferred for chronic pain. OT = opioid therapy; PDMP = prescription drug monitoring program; SUD = substance abuse disorder; UDT = urine drug test; VA/DoD Suicide CPG = US Department of Veterans Affairs/US Department of Defense "Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide."

OUD for patients on LOT was 34.9% (based on DSM-5 criteria) and 35.5% (based on DSM-4 criteria).

The CDC guideline does not specifically address this issue.

Initiation or Continuation of Opioid Therapy in Patients Younger than Age 30 Years

Recommendation 6

a. We recommend against long-term opioid therapy for patients younger than age 30 years secondary to higher risk of opioid use disorder and overdose. (Strong against)
b. For patients younger than age 30 years currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits. (Strong for)

All patients who chronically take opioids for pain are at risk for OUD, especially those who are younger than age 30 years. This is of particular concern in the DoD and VA patient populations due to the increased frequency of chronic pain secondary to injury relative to the general population. Six studies were identified that examined age as a predictor of OUD, respiratory/central nervous system depression, and/or overdose; four of the six studies were rated as moderate-quality evidence [13,15–17]. Two were rated as low-quality evidence [18,19]. Five studies demonstrated that age was inversely associated with the risk of OUD and overdose [13,15–17,19]. One study showed that older subjects had a higher hazard ratio (HR) of overdose, but this study was of low quality [18]. Therefore, the Work Group's overall confidence in the quality of the evidence was judged as moderate.

Similar to other risk factors, age younger than 30 years should be weighed heavily in the risk-benefit calculus for initiating LOT. Age younger than 30 years is not an absolute contraindication to LOT as there may be some situations where the benefits of LOT clearly outweigh the risks of OUD and overdose. Hospitalized patients recovering from battlefield injuries, for example, are known to have less chronic pain, depression, and posttraumatic stress disorder (PTSD) when their pain is aggressively managed starting soon after injury [20]. In those cases, LOT may be appropriate only if risk mitigation strategies are employed and patients are titrated off LOT as soon as it is appropriate.

The added risk younger patients using opioids face for OUD and overdose (in comparison with older patients) is significant. Edlund et al. (2014) [13] found that subjects age 18 to 30 years carried 11 times the odds of OUD and overdose in comparison with those older than age 65. Furthermore, Bohnert et al. (2011) [15] found that subjects older than age 70 years had a substantially lower chance of developing OUD or overdose (HR = 0.06) in comparison with subjects in the 18–29 years age category.

Younger patients are also at a higher risk of opioid misuse (as suggested by a UDT indicating high-risk medication-related behavior). Turner et al. (2014) [21] showed patients in the 45–64 years age group were significantly less likely to have an aberrant UDT (detection of a nonprescribed opioid, nonprescribed benzodiazepine, illicit drug, or tetrahydrocannabinol [THC]) in comparison with patients in the 20–44 years age group. Patients in the 45–64 years and 65 years and older age groups were significantly less likely than the 20–44 years age group to have nondetection of a prescribed opioid as well (indicating possible diversion) [21]. Further supporting this recommendation is evidence in other areas that shows that developing brains (age < 30 years) are at increased risk of addiction when exposed to addictive substances early in life [22–25].

The CDC guideline states, "Factors associated with increased risk for misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications" but does not particularly identify a restrictive age in the consideration of opioid therapy.

Concurrent Sedatives

Recommendation 5

We recommend against the concurrent use of benzodiazepines and opioids. (Strong against)

Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate.

Harms outweigh benefits for the concurrent use of benzodiazepines and LOT. There is moderate-quality evidence that concurrent use of benzodiazepines with prescription opioids increases the risk of overdose and overdose death [26,27]. In a retrospective cohort study, the adjusted odds ratio (AOR) for drug overdose was highest for individuals on LOT for chronic pain who also received concurrent long-term benzodiazepine therapy [26]. Furthermore, there is a lack of evidence in favor of long-term therapy with benzodiazepines and opioids for chronic pain [28].

Once initiated in combat veterans, benzodiazepines can be very difficult to discontinue due to withdrawal, which is often compounded by ensuing exacerbations of PTSD symptoms. Moreover, abrupt discontinuation of benzodiazepines should be avoided as it can lead to serious adverse effects including seizures and death. Tapering benzodiazepines should be performed with caution and within a team environment when possible [29].

In addition to benzodiazepines, the addition of other psychoactive medications to LOT must be made with caution. We suggest not prescribing "Z-drugs" (e.g., zolpidem, eszopiclone) to patients who are on LOT as moderate-quality evidence demonstrates that the combination of zolpidem and opioids increases the AOR of overdose [26]. The evidence reviewed also identifies potential adverse outcomes (e.g., risk of overdose) with the combined use of antidepressants and opioids in patients who do not have depression [26]. This particular study did not differentiate between classes of antidepressants, limiting the ability of the Work Group to recommend for or against prescribing opioids and a specific class of antidepressants. As such, there is no specific recommendation with respect to using specific classes of antidepressants and LOT.

The CDC guideline states, "Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible." This statements is similar, however, to the CDC Guideline, which states, "The clinical evidence review did not address risks of benzodiazepine co-prescription among patients prescribed opioids. However, the contextual evidence review found evidence in epidemiologic series of concurrent benzodiazepine use in large proportions of opioid-related overdose deaths." This guideline did review the evidence in making our recommendation.

Risk Mitigation

Recommendation 7

We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include:

- ongoing, random urine drug testing (including appropriate confirmatory testing);
- checking state prescription drug monitoring programs;
- monitoring for overdose potential and suicidality;
- providing overdose education;
- prescribing of naloxone rescue and accompanying education. (Strong for)

A paradigm shift occurred in the approach to ensuring and documenting patient and provider understanding and expectations regarding the risks and benefits of LOT. While the prior paradigm allowed for opioid therapy agreements (also known as opioid contracts), the realized increased risk and ethical concerns have replaced agreements with an informed consent process. Refusal of this process by the patient may lead to changes in whether to proceed with LOT.

The confidence in the quality of the evidence was moderate for UDT and frequent follow-up and was low for opioid treatment agreements/informed consent. The frequency of follow-up and monitoring should be based on patient level of risk as determined by an individual risk assessment.

Implementing more extensive risk mitigation strategies entails an investment of resources. Primary care providers may require more time with patients to shared decision-making and treatment planning. More frequent follow-up of patients on LOT can affect access to care for all empaneled patients.

The CDC guideline has risk mitigation split into several sections. It states, "When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually." It also states, "Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months." These are in agreement with our guideline. The CDC guideline also states, "Although the clinical evidence review did not find studies evaluating the effectiveness of written agreements or treatment plans (KQ4), clinicians and patients who set a plan in advance will clarify expectations regarding how opioids will be prescribed and monitored, as well as situations in which opioids will be discontinued or doses tapered." Our guideline specifies informed consent as required with any medical procedure/medication with a higher level of risk.

Our guideline recommends the coprescription of naloxone rescue and accompanying education as a risk mitigation strategy based on 22 observational studies but recognizes that clinical efficacy has not been established for the use of methadone or exceptionally potent opioids. It also notes that multiple doses maybe required for some overdoses.

In regards to naloxone rescue, the CDC guideline did not research naloxone's efficacy but states, "Most experts agreed that clinicians should consider offering naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids, patients at risk for returning to a high dose to which they are no longer tolerant, and patients taking higher dosages of opioids (≥50 MME/d). Practices should provide education on overdose prevention and naloxone use to patients receiving naloxone prescriptions and to members of their households."

Risk Mitigation—Suicidality

Recommendation 8

We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary. (Strong for)

Every suicide is a tragic outcome. According to the VA-DoD 2013 "Assessment and Management for Patients at Risk for Suicide," 22% of all suicides occur in veterans [30]. They further state that rates of suicide in the population of veterans using the VA health care system are higher than those of the general population and especially higher in those with a mental health diagnosis. The Va-DoD 2013 suicide guideline stresses removing lethal means from the suicidal patient's environment for those in the moderate or severe risk categories. Opioid prescriptions are one of those possible means. This suggestion is supported by a large retrospective observational study in veterans that found increased levels of risk with increased dose. Compared with patients receiving 20 or fewer milligrams per day (mg/d), hazard ratios were 2.15 for 100+ mg/d [31]. This evidence was not causal as the patients on higher doses could have more poorly treated pain. The issue is complicated by pain being an independent suicide risk factor [32,33].

Based on this information, the Work Group recommended that suicide be assessed or reassessed at each step of opioid therapy. It was given a grade of strong for, with moderate evidence supporting increased monitoring as being protective for suicide attempts.

The CDC guideline mentions suicide attempts or risks as a factor in using opioid therapy, but it does not specifically advocate monitoring.

Dose, Follow-up, and Taper of Opioids

Recommendation 10

If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits. (Strong for)

Note: There is no absolutely safe dose of opioids.

Recommendation 11

As opioid dosage and risk increase, we recommend more frequent monitoring for adverse events, including opioid use disorder and overdose. (Strong for)

Note: Risks for opioid use disorder start at any dose and increase in a dose-dependent manner. Risks for overdose and death significantly increase at a range of 20–50 mg morphine equivalent daily dose.

Recommendation 12

We recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain. (Strong against)

Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation.

There is moderate-quality evidence from retrospective cohort and retrospective case-control studies indicating that risk of prescription opioid overdose and overdose death exists even at low opioid dosage levels and that it increases with increasing doses. Significant risk (approximately 1.5 times) exists at a daily dosage range of 20 to less than 50 mg morphine equivalent daily dose (MEDD) and further increases (approximately 2.6 times) at a range of 50 to less than 100 mg MEDD compared with the risk at less than 20 mg MEDD. Risk continues to increase at higher dosage ranges (≥100 mg MEDD) [15,18,26,34]. In a prospective cohort study (not included in the evidence review as it did not include information on acute vs chronic pain in the patient population), Dasgupta et al. (2015) [35] compared residents of North Carolina who had received an opioid prescription in the last year to residents who had not. The study examined the outcome of population-based rates of opioid overdose mortality by opioid dose, without use of a presupposed threshold. There was no safe dose of opioid. Among the more than nine million individuals followed for one year, 629 died from opioid overdose. Of these 629 individuals, 151 had no record of having been dispensed an opioid. Of the 478 patients who died from an opioid overdose who were prescribed opioids, 235 (49%) had been prescribed less than 80 mg MEDD. Overdose incidence rate ratios (IRRs) doubled each time the MEDD ranges increased from 60.0–79.9 mg to 80.0–99.9 mg (IRR = 2.9 to 6.2), then to 120–139.9 mg (IRR = 14.1), 160–179.9 mg (IRR = 29.5), and 350–399.9 mg (IRR = 63.2).

The CDC guideline recommendations are very similar, with 50 and 90 MEDD dose limits.

Opioid Tapering

Recommendation 14

We recommend tapering to reduced dose or discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits. (Strong for)

Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.

LOT use should be regularly reassessed by clinicians, with consideration of tapering or discontinuation when

the risks exceed the benefits of therapy. Observational studies suggest that when opioids are tapered or discontinued within the context of a multimodal pain rehabilitation care plan, patients can experience an improvement in their pain, function, and mood [36,37]. Nonpharmacologic therapies and nonopioid pharmacologic therapies are preferred and should be optimized. Several factors should be taken into consideration when determining the balance of risks and benefits of OT, recognizing that multiple risk factors increase cumulative risk [38,39]. These factors include concerns about OUD or substance use disorder (SUD), medical or mental health conditions that increase risk, concomitant medications that increase overdose risk, unmanageable side effects, and lack of clinically meaningful improvement in function. Abrupt discontinuation of opioids may be justified in certain high-risk circumstances. When there is evidence for diversion, the clinician may need to discontinue OT and frequently assess for withdrawal symptoms. The tapering treatment plan should be individualized and should address the pace of tapering, setting of care, and frequency of follow-up. Low frequency of follow-up in primary care and limited access to comprehensive interdisciplinary specialty pain, rehabilitation, mental health, and addiction services may be barriers to tapering LOT. Tapering may unmask underlying OUD. Therefore, frequent assessment for OUD is recommended.

The rate of taper takes into account several factors, including initial dose, formulations available, and risk factors that increase harm. A gradual taper over months, or even years, with 5% to 20% dose reduction every four weeks is indicated for higher opioid doses and/or longer duration of OT. In some patients, a faster taper, such as a 5% to 20% reduction per week, may be needed when risks are too high to consider a gradual taper. Specialty consultation should be obtained if the risks warrant a more rapid taper. Such risks include nonadherence to the treatment plan and escalating high-risk medication-related behaviors. These patients will need frequent follow-up and reevaluation of SUD, mental health, and/or co-occurring medical conditions with every dose change. It should be recognized that elevated dose alone poses increased risk of overdose, overdose death, adverse effects, and the development of OUD.

A biopsychosocial assessment including evaluation of medical, psychiatric, and co-occurring substance use conditions, as well as the patient's social support system, should be completed prior to the initiation of an opioid taper. The risks and benefits of the current opioid regimen should be weighed with the risks and benefits associated with a reduction in opioid dose. Follow-up should occur within a range of one week to one month after any opioid dosage change and should include education about self-management strategies and the risks associated with OT.

Clinicians should consider using an interdisciplinary, team-based approach that may include primary care, mental health, pain specialty/rehabilitation, physical therapy, and/or SUD services during the opioid tapering process. Additional research is needed to identify the opioid tapering processes that are associated with the best patient outcomes among a broad range of domains including general functioning, psychosocial functioning, mood, pain-related disability, and adverse outcomes assessed in the short, medium, and long term.

The CDC guideline has a similar section on tapering entitled "Considerations for tapering opioids" and a similar finding of nonsuperiority of one method over another.

Recommendation 17

We recommend offering medication-assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder. (Strong for)

Note: See the VA/DoD "Clinical Practice Guideline for the Management of Substance Use Disorders."

OUD is associated with premature death from opioid overdose and other medical complications such as acquired immunodeficiency syndrome (AIDS), hepatitis C, and sepsis. On average, OUD carries a 40% to 60% 20-year mortality rate [40]. Persons with OUD are at high risk for premature death, not only from opioid overdose but also from other consequences. Thus, providing firstline treatment is important to save lives as well as to improve the quality of life.

Strong evidence supports the use of opioid agonist therapy (e.g., methadone, buprenorphine/naloxone) as firstline treatment for moderate to severe OUD. One multicenter RCT tested patient responses to tapering of buprenorphine/naloxone to discontinuation over four to 12 weeks, plus two regimens of outpatient counseling [40]. The results of the study suggest that medication-assisted treatment (MAT) with buprenorphine/naloxone and brief structured counseling by the prescribing physician can be successful for about half of selected patients with prescription OUD, whereas withdrawal management alone, even with close weekly follow-up and counseling, is successful for less than 10% of patients. Furthermore, the presence of chronic pain does not seem to interfere with the success of MAT, based on the conclusions of an RCT by Weiss et al. (2011) [41] and a meta-analysis by Dennis et al. (2015) [42].

Given the high mortality associated with OUD and the safety and efficacy of MAT for OUD in multiple clinical trials and meta-analyses, we recommend MAT for those who meet DSM-5 criteria for OUD. Those who do not respond to minimal counseling may benefit from a comprehensive assessment and more intensive treatment of

OUD and any co-occurring conditions in SUD specialty care settings.

On this subject, the CDC guideline states, "Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder." There is agreement between the two guidelines.

Recommendation 18

a. We recommend alternatives to opioids for mild to moderate acute pain. (Strong for)
b. We suggest use of multimodal pain care including nonopioid medications as indicated when opioids are used for acute pain. (Weak for)
c. If take-home opioids are prescribed, we recommend that immediate-release opioids are used at the lowest effective dose, with opioid therapy reassessment no later than three to five days later to determine if adjustment or continuing opioid therapy is indicated. (Strong for)

Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.

The VA-DoD guideline targets the contribution of opioids given for acute pain therapy leading to prolonged use of opioids and the risks accompanying their use. They did not evaluate the benefits compared with risks of acute opioid therapy nor the efficacy of alternative treatments for mild to moderate pain, even though they are recommended. They cite Halbert et al. [43] and Deyo et al. [44], who looked at opioid prescribing in a medical population. Deyo et al.'s study of 536,767 patients found that 5% of those who received six or more refills became chronic users, with rural location, prescription of long-acting medications, and increased age being other risks. Halbert et al. focused on the contribution of mood disorders and a more than twofold increase in numbers of patients transitioning to chronic use in those with mood disorders. The above medical studies and three surgical studies [45–47], one using postoperative hip, postoperative knee, and general postoperative populations, were cited as identifying duration of use as risk factors leading from acute use to LOT. Overdose risks as described by Bohnert et al. [15] and Zedler et al. [18] were also cited as reasons to reassess acute opioid use in three to five days.

The reasoning for using a reassessment in three to five days was not detailed in the discussion section of this recommendation.

The CDC guideline states, "When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed." These guidelines are in concordance in regards to acute use leading to LOT and the risks thereof and to not using long-acting medications for acute pain. There is a difference in acute use risk mitigation, with the CDC favoring limitation of prescription to three days with a seven-day provision for outliers, compared with a three- to five-day reassessment. This softer recommendation may have been due to a lack of data on the efficacy of the acute use of opioids, making it harder to balance risk and benefits.

Discussion

While there is a significant amount of concordance between this guideline and the CDC guideline [3], they differ in a few critical aspects. The CDC guideline uses expert determination and focuses on the overdose and death prevention end points in making their recommendations while this guideline is evidence determined and additionally gives consideration to recent data relating to the development of substance use disorder as a major end point. Further major differences perhaps more relevant in the unique VA-DoD population are the specific avoidance of LOT for patients younger than age 30 years due to the risk of abuse or overdose, a stronger avoidance of concurrent benzodiazepine use recommendation, a focus on suicide prevention, a short-term reassessment strategy for acute pain, and a specific three-month time frame to prevent transition from less than three months to long-term therapy.

This guideline also requires the use of informed consent as part of the prescribing risk mitigation process, whereas the CDC passed on the use of either informed consent or agreements. The comprehensive risk mitigation strategy also includes ongoing random urine drug testing, providing overdose education, suicide prevention, and prescribing naloxone rescue medications. Interdisciplinary management should be instituted for all chronic pain patients to address the problem through multiple modalities, with the overall goal of reducing opioid requirement and using nonpharmacologic and nonopioid pharmacologic methods as the preferred method for treatment of chronic pain. This approach may require increased resources that could impact all enrolled patients, but the level of risk suggests strong measures as required.

This guideline's creation was unique compared with other nonopioid guidelines. After the key questions were developed and researched, the US Congress passed the CARA Act, requiring us to consider the CDC guideline in writing our guideline. The CDC guideline development was helpful in identifying areas of concern and taking the backlash from patients, industry, and practitioners invested in opioid therapy.

Second, as this was a guideline renewal, we had only a limited number of questions that we could ask, despite the large amount of new studies. Careful construction of the key questions mitigated these concerns.

Table 1 VA/DoD OT CPG recommendations

#	Recommendation	Strength*	Category†
Initiation and Continuation of Opioids			
1.	a. We recommend against initiation of long-term opioid therapy for chronic pain. b. We recommend alternatives to opioid therapy such as self-management strategies and other nonpharmacological treatments. c. When pharmacologic therapies are used, we recommend nonopioids over opioids.	a. Strong against b. Strong for c. Strong for	Reviewed, new-replaced
2.	If prescribing opioid therapy for patients with chronic pain, we recommend a short duration. Note: Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits.	Strong for	Reviewed, new-added
3.	For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies (see Recommendations 7–9), assessment for opioid use disorder, and consideration for tapering when risks exceed benefits (see Recommendation 14).	Strong for	Reviewed, new-replaced
4.	a. We recommend against long-term opioid therapy for pain in patients with untreated substance use disorder. b. For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, we recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering (see Recommendations 14 and 17).	a. Strong against b. Strong for	Reviewed, amended
5.	a. We recommend against the concurrent use of benzodiazepines and opioids. Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate (see Recommendation 14 and VA/DoD substance use disorders CPG).	Strong against	Reviewed, new-added
6.	a. We recommend against long-term opioid therapy for patients younger than age 30 years secondary to higher risk of opioid use disorder and overdose. b. For patients younger than age 30 years currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits (see Recommendations 14 and 17).	a. Strong against b. Strong for	Reviewed, new-replaced
Risk Mitigation			
7.	We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include: • ongoing, random urine drug testing (including appropriate confirmatory testing); • checking state prescription drug monitoring programs; • monitoring for overdose potential and suicidality; • providing overdose education; • prescribing of naloxone rescue and accompanying education.	Strong for	Reviewed, new-replaced
8.	We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary.	Strong for	Reviewed, amended

(continued)

Additionally, the CARA Act required us to add two sections, naloxone rescue and acute pain prescriptions leading to LOT, which had been initially overlooked. So, it is not surprising that this guideline is comparable with the CDC guideline, with largely corresponding areas of concern.

The guideline renewal rules complicated the process in that there are different evidentiary rules regarding prior recommendations as opposed to new recommendations. However, there were no 2010 recommendations that made it into the 2017 guideline unchanged or unresearched. Finally, the regulations regarding opioid therapy vary on a state-to-state basis, and while the VA and DoD practice within a federal framework, the practitioners' licenses are granted on a state basis, guiding their practice. The use of outside practitioners through contracts or fee for service complicates matters further.

Some may consider the strength of recommendation for some of these recommendations to be too high. It bears repeating that the weight of the evidence for harms was consistently much greater than the evidence of benefit. The paradigm shift is profound from the 2003 VA-DoD opioid therapy guideline, in which opioid therapy was advocated, to the 2010 opioid therapy guideline, in which we advocate for careful use when nothing else works, to this current guideline, in which chronic opioid therapy is to be avoided, even when other treatments don't work. Most of us have patients whom we have successfully managed for years with moderate doses of opioids. It is difficult to accept science that conflicts with our clinical experience and may prompt patients who have been accustomed to more liberal opioid prescribing to object to risk mitigation or thoughtful tapering and even leave the clinic. Panel members too felt this angst, and every effort was made to minimize these potential disturbances, cautioning against abrupt discontinuation and patient abandonment and advocating for suicide assessment and alternative treatment availability. We were concerned that readers would concentrate too tightly on the recommendations and not read the discussion, so notes of caution were inserted into the recommendations. We added patient education via a patient summary guide, explaining how the science of opioid therapy is changing and the new understanding of opioid risks. While pain management strategies should be individualized based on the unique challenges and preferences for each patient, these guidelines highlight the importance of the conservative use of LOT for non-end-of-life chronic pain due to the lack of evidence for benefit combined with the risk of side effects and OUD. We also recognized that these guidelines could be used to standardize care. The benefits of standardization should be administered lightly, allowing for optimal pain care, respectful of patient preferences when possible.

Finally, medical guidelines are only as good as the evidence and the providers. State and national laws are also rapidly changing. This guideline may need to be changed as new studies are reported. We can look forward to new studies examining LOT, the effects of mitigation strategies, and the development of novel medications and therapies. These examples of future science will shape pain medicine and our guidelines.

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